REMARKS

Reconsideration and allowance is respectfully requested.

Upon entry of this Amendment, claims 1-25, as amended, and new claim 26, will be pending, of which claims 1, 14 and 22 are independent. None of the claim amendments introduce new matter into the application.

As explained below, new claim 26 is directed to subject matter which encompasses the embodiment of Applicants' invention which is believed to correspond to the subject matter which the Examiner has acknowledged is adequately described by the written description and is based on an enabling disclosure. However, as will be explained in further detail below, all of the pending claims are supported by an adequate disclosure which, coupled with the skill and knowledge of the practitioner would enable the person of ordinary skill in the art to practice the claimed invention.

The thoroughness of the Office Action is appreciated and Applicants have made a sincere effort to comply with the Examiner's suggestions for eliminating claim objections and rejections in paragraphs 7-22. These claim amendments will be discussed below.

At the outset, however, Applicants, acknowledge with appreciation that the pending claims are considered to be free of the prior art. Accordingly, the claims have been amended to avoid the assertions of indefiniteness and to remove claim objections. However, none of the foregoing amendments was intended to substantively narrow the scope of the claims in any respect.

The various parts of the **DETAILED ACTION** will be considered in the order in which each section appears.

Status of the Application

Applicants do request reconsideration of the restriction and withdrawal of claims 14-25.

The stated basis for the distinctness between claims 1-13 (Group I) and claims 14-21 (Group II), *i.e.*, that the DNA fragments could not be made nor used by the method of Invention I, is not entirely correct. When the DNA fragments are inserted into a microorganism, the non-ribosomal dipeptide synthetase can be expressed and used in the method of Group I.

The asserted distinction between the product of claims 22-25 is that a DNA fragment coding for $(Asp\text{-}Phe)_n$ in a ribosomal fermentative route can be used to produce Asp-Phe. However, even if so, Groups III and I do not relate to a DNA fragment coding for $(Asp\text{-}Phe)_n$ but to non-ribosomal DNA fragments coding for the dipeptide Asp-Phe (*i.e.*, n = 1, only). Group I relates to a method for production of Asp-Phe and Group III relates to non-ribosomal Asp-Phe dipeptide synthetase (see the above amendments to claims 22-25) which may be used in the process.

With regard to Group II and Group III, the assertion that the protein can be made by another process such as chemical synthesis is not deemed to be credible under the current state of the art.

Accordingly, it is respectfully submitted that all of the pending claims are related and should be examined in this application. Therefore, rejoinder of Groups II and III with Group I is respectfully requested.

Specification

1. The specification is objected to for not complying with the sequence rules. Accordingly, the specification is amended to include sequence identifiers for each of the sequences and to include a Sequence listing together with a computer-readable form of same. Also enclosed is a Statement to Support Filing and Submission in Accordance with 37 C.F.R. §§ 1.821-1.825. No new matter is added.

2. The specification is objected to due to the presence of a blank space in page 21. Appropriate correction has been required.

However, the appropriate correction is not immediately apparent. The blank space on page 21 is an intentional blank space, the text continuing with the new section DNA FRAGMENTS ENCODING AN Asp-Phe DIPEPTIDE SYNTHETASE, ETC., which begins at the top of page 22.

Nevertheless, in attempt to respond to the objection the specification on page 21 is amended by adding, following the paragraph beginning on line 3, the text: "THIS SPACE IS INTENTIONALLY LEFT BLANK." If some other response is more appropriate, Applicants would be willing to comply.

Priority

3/4/5. The acknowledgement of the claim for foreign priority and receipt of all certified copies of the priority documents as well as the acknowledgement of the claim for Domestic priority under 35 U.S.C. 119 and 120 and/or 121, are appreciated.

Information Disclosure Statement

6. The return of the initialed and dated Form PTO-1449 is also appreciated.

Claim Objections

7. "Method for" is changed to --A method for--.

8. The phrase "containing thiolation domain" is believed to be correct, however, for further clarity the phrase is replaced with --a thiolation domain containing a 4'-phosphopantetheinyl cofactor --.

9. The term "micro-organism" is changed to --microorganism--.

10. The semicolons (;) in claims 6 and 8 are replaced, when appropriate, with commas (,).

11. The phrase "mixtures thereof is being fed" is changed to --a mixture thereof-- and the words "is fed being" are omitted as further discussed below.

The changes referred to in paragraphs 6-11 are not intended to narrow the scope of the claims.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

14. The term "microbiological" is deleted from claim 1 and the title and portions of the specification are correspondingly changed. As noted from the entire disclosure, the practice of the invention method may, but need not, include microbiological production (*see, e.g.*, claims 6-10 for embodiments using microbiological production versus claim 11 for an embodiment not requiring microbial production).

15. Although Applicants do not agree that the references to "of these modules" could logically have been understood to refer to anything other that the previously recited "minimal modules" for further clarity and explicitness, claim 1 is amended to recite, --N-terminal module of these <u>minimal</u> modules-- and --C-terminal module of these <u>minimal</u> modules--.

The term "is covalently bound at its N-terminal end" is believed to clearly and unambiguously refer to the N-terminal end of the C-terminal module.

The term "and that the ... formed is recovered" has been replaced by language which more clearly correlates such term with what is recited previously in the claim.

It should be noted that the Examiner's suggestion of what claim 1 is directed to for examination purposes has been taken into consideration in amending claim 1.

The foregoing amendments are presented for clarification and are not intended to narrow the scope of the original claims.

16. The language considered indefinite in claim 2 is amended by deleting the expression "connected to both minimal modules in such way that it is" such that claim 2 now reads: -- wherein the condensation domain in the dipeptide synthetase is also covalently bound to the module recognizing L-aspartic acid.--

Thus, the expression "covalently bound to the module recognizing L-aspartic acid" further limits claim 1 since in claim 1 only the second minimal module (recognizing L-Phe) is required to be covalently bound. In claim 1, the minimal domain recognizing L-Asp does not need to be covalently bound to the condensation domain. Thus, claim 2, which is directed to this embodiment of the invention, does further limit claim 1.

17. With regard to claim 3, the following language has been adopted, consistent with the Examiner's understanding of the intended meaning of the claim: "wherein the non-ribosomal dipeptide synthetase further comprises a thioesterase releasing factor for the Asp-Phe formed." This clarifying language overcomes the rejection in this paragraph.

18. Claim 4 as modified now depends from claim 3 and provides a more meaningful description of "integrated domain" (which terminology is no longer used) to reflect that the integration refers to covalent binding at the C-terminus of the dipeptide synthetase. Accordingly, as amended, claim 4 includes the embodiment wherein the condensation domain is covalently bound to the module recognizing L-aspartic acid (*see, also*, claim 2) as well as that the thioesterase releasing factor is covalently bound to the module recognizing L-phenylalanine. See also claim 25 where similar changes appear.

Accordingly, the rejection in this paragraph is avoided without changing the meaning or scope of the claim.

Accordingly, the rejection of this paragraph has been avoided.

19. The non-integrated protein includes proteins with thioesterase Type-II activity. The non-integrated protein may be a separate protein.

Accordingly, the rejection in this paragraph is respectfully traversed and/or avoided.

20. The language of claim 6 is revised to eliminate any potential confusion as well as to provide antecedent basis for "said fermentor." The redundant phrase is no longer present.

Accordingly, the rejection in this paragraph is avoided.

21. The language of claim 7 is modified to eliminate any potential ambiguity or lack of clarity, again conforming to the Examiner's understanding of the meaning of this claim.

22. Finally, in this section, claim 11 is modified to avoid any potential ambiguity or lack of clarity. Thus, claim 11 is directed to the embodiment of the invention wherein the production of Asp-Phe is carried out in the presence of the dipeptide synthetase in its isolated form in a reactor and simultaneously supplying L-Asp, L-Phe, or mixture thereof and ATP to the reactor (*see, e.g.,* page 7 lines 15-18).

Accordingly, the rejection in this paragraph is avoided.

While, as noted above, claims 14-25 are withdrawn from consideration, in order to materially advance prosecution, these claims are amended, similarly to the amendments in claims 1-13, to overcome any potential formal grounds of rejection and to facilitate rejoinder of these claims. For example, the language of claim 16 clarifies that the releasing factor is a "thioesterase releasing factor" and 17 is amended to provide greater clarity, noting that the DNA fragment according to the embodiment of the invention to which this claim is addressed is the fragment with the two covalent bonds described.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

24. Applicants respectfully disagree that the specification does not include a written description of the claimed subject matter wherein a genus of non-ribosomal dipeptide synthetases is used.

The written description does convey that Applicants were in possession of the invention to which the claims are directed.

The specification does, by specific example, and by general descriptions (*see, e.g.,* pages 4- 6) set forth the functional and structural properties of non-ribosomal peptide syntheses which are applicable to non-ribosomal dipeptide synthetases. One skilled in the art would have no difficulty in ascertaining whether any particular structure functions as non-ribosomal dipeptide synthetase. The specification provides detailed descriptions of the minimal modules which exist at clearly defined positions within the context of the larger non-ribosomal peptide synthetases. These have very characteristic structures, also at the level of the amino acid sequence of the protein produced. As described, the mechanism of the non-ribosomal peptide synthetase production of peptides is a co-linear synthesis mechanism. The modules have clearly distinguishable "domain limits."

This is not a case where the meaning of "minimal modules" or the components and functions thereof were not known at the time of the invention. In the embodiment of the present invention under consideration (Asp-Phe) is prepared by contacting L-Asp and L-Phe as substrates, in the presence of an effective amount of ATP, with a non-ribosomal dipeptide synthetase, one minimal module recognizing L-Asp, the other recognizing L-Phe. Furthermore, it is the N-terminal of these minimal modules that recognizes L-Asp and the C-terminal which recognizes L-Phe.

Nor is this a case where the minimal modules and/or the component parts thereof are described by only functional utility. The disclosure of this application provides identification of specific structural components of each of the identified modules. Here, the "generic" claims do not encompass merely any dipeptide synthetase but only those non-ribosomal dipeptide synthetases wherein the N-terminal module recognizes L-Asp and the C-terminal module recognizes L-Phe and further wherein the two minimal modules are connected by a condensation domain to which the C-terminal is covalently bound at its N-terminal. Still further, each minimal module is composed of an adenylation domain and a 4'-phosphopantetheinyl cofactor containing a thiolation domain. The specification (*see, e.g.,* Table, page 9) provides examples of core motifs and consensus sequences of each of the adenylation domain, the thiolation domain, the condensation domain, as well as the thioesterase domain.

Moreover, in this case, the Examiner has acknowledged an acceptable written description of specific embodiments of non-ribosomal dipeptide synthetases which may be successfully used in the production of Asp-Phe, namely, the production of Asp-Phe using (1) hybrid Asp-Phe dipeptide synthetase encoded in part by DNA comprising part of the *srfB* gene from *B. subtilis* ATCC 21332 and in part being encoded by DNA comprising part of the *tyc*A gene from *B. brevis* ATCC 8185 coding for a Phe minimal module (adenylation (A) and thiolation (T) domain), and (2) a hybrid as described in (1) further comprising what appears to be a thioesterase domain from B. subtilis ATCC 21332, *see*, page 9 of Office Action). New claim 26 encompasses this embodiment and should be allowable; however, for the reasons explained herein, all of the pending claims are believed to be allowable.

Under these circumstances, and taking into consideration that the present Applicants were the first to discover and report that the dipeptide Asp-Phe could be produced using non-ribosomal dipeptide synthetases, the specification does include enough detail for one of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed. Cf. *University of Rochester v. G.D. Searle & Co., Inc.*, 68 USPQ2d 1424 (DC WDNY 2003) which involved a situation wherein there was no evidence "that the inventors had identified so much as one compound that would be suitable for use in practicing the claimed invention."

The present case should be governed by *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385 (Fed. Cir. 2003). In *Amgen* the court distinguished the written description cases which required more than a mere description of function alone to satisfy Section 112, from the case where the claims do not require new or unknown biological materials that ordinarily skilled artisans would easily misunderstand.

In the present case, the minimal modules each include an adenylation domain and a 4'-phosphopantetheinyl cofactor containing-thiolation domain. Each of these types of functional domains were known at the time of the invention and would not be easily misunderstood by ordinarily skilled artisans. Each was exemplified by specific structures not merely by function.

As explained in the first full paragraph of page 8 of the specification the adenylation domain and the thiolation domain, "together form the smallest part of a module that retains all catalytic activities for specific activation and covalent binding of the amino acid

substrate." The disclosure explains that highly conserved core motifs of adenylation and thiolation domains are known to exist in peptide synthetases, and several are listed in table 1. The specification goes on to further describe the adenylation domain (pages 8-10) and the thiolation domain (pages 10-11).

The specification also provides more detailed information regarding the condensation domain (*see, e.g.*, paragraph bridging pages 11 and 12). Similar further details are provided for the thioesterase releasing factors and the thioesterase Type II proteins (*see, e.g.*, pages 12-15).

Thus, while prior to the present invention, it was not known to apply non-ribosomal Asp-Phe synthesis, the body of art relating to non-ribosomal peptide syntheses provides ample information of the components of such non-ribosomal Asp-Phe dipeptide synthetases for the production of Asp-Phe to convince the artisan that Applicants were in possession of the claimed invention.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-13, under the first paragraph of 35 U.S.C. 112, for lack of written description, is respectfully requested.

25. For substantially the same reasons why the specification satisfies the written description requirement, the specification also satisfies the enablement requirement. Again, the rejection does not assert that there is not enablement for at least the exemplified embodiments. However, it is asserted that undue experimentation would be required to practice the entire scope of the claimed invention.

Again, Applicants respectfully disagree.

As stated above, each of the components of the minimal modules of the peptide synthetases are known in the art and those skilled in the art would be able to refer to the existing literature to find additional examples of each of the respective components of the minimal module as well as the additional optional or preferred components.

While there has been reference to structural homology, it is not believed that structural homology is at issue with respect to enablement. One need only refer to the known existing adenylation domains, thiolation domains, condensation domains, thioesterase releasing factors and thioesterase Type II proteins for constructing Asp-Phe producing non-

ribosomal dipeptide synthetases which would enable the practice of the present invention. For example,

(1) colinearity (of the peptide synthetase molecule, and of the molecule formed therewith) is known to exist for known peptide synthetases [*e.g., see*, van Sinderen *et al*, Mol. Microbiology (1993), p. 833-841, "Characterization of the *srfA* locus of *Bacillus subtilis* : only the valine-activating domain of *srfA* is involved in the establishment of genetic competence." This article (copy enclosed) recites in the summary: "... These results indicate colinearity between the order of the domains in the *srfA* locus and the amino acid sequence of surfactin. ..."].

(2) In the enclosed article by Konz, *et al*, Chemistry & Biology, February 1999, pages R39-48 (see, for example, Table 1, page R42) primary structures (amino acid sequences) of peptide products are shown in combination with the deduced domain structures of peptide synthetases (PPS) corresponding therewith. In particular, these include Asp and Phe recognizing modules, *e.g.,* the PPS corresponding to syringomycin.

(3) The person of ordinary skill in this art can relatively easily establish whether a particular module recognizes L-Asp or L-Phe or any other amino acid.

Therefore, although some experimentation may be required to combine the respective elements of the minimal modules of the non-ribosomal dipeptide synthetase, the experimentation would not be undue given the guidelines provided in the specification and the general level of skill in the art.

Accordingly, reconsideration and withdrawal of the non-enablement rejection is respectfully requested.

26. It is respectfully submitted that all of the pending claims are in condition for allowance.

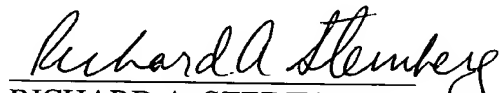
27. A clean copy of the pending claims is appended to this paper.

It is respectfully submitted that the Application is in condition for allowance and a Notice to that effect is courteously solicited.

If any questions remain, however, the Examiner is encouraged to call Applicants' undersigned representative to expedite the prosecution of this Application.

Respectfully submitted,

PILLSBURY WINTHROP LLP



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Attachment: Statement to Support Filing
Sequence Listing (paper copy and diskette)
Clean copy of currently pending claims